PRODUCT MONOGRAPH

phl-NIZATIDINE

(Nizatidine Capsules phl Standard)

Capsules, 150 and 300 mg

Histamine H_2 Receptor Antagonist

Pharmel Inc.
8699 8th Avenue
Montreal, Quebec
H1Z 2X4

Date of Preparation:
November 5, 2004

Control No: 095052

NAME OF DRUG

phl-NIZATIDINE

(Nizatidine Capsules phl Standard 150 mg and 300 mg)

THERAPEUTIC CLASSIFICATION

Histamine H_2 Receptor Antagonist

ACTION

Nizatidine is a competitive, reversible inhibitor of the histamine H_2 receptor of gastric-acid secreting cells. Nizatidine is not an anticholinergic agent. It inhibits nocturnal gastric-acid secretion as well as gastric-acid secretion stimulated by food, caffeine, betazole and pentagastrin. Pepsin output is reduced in proportion to the reduced volume of gastric secretions. Nizatidine has little or no effect on basal serum gastrin or food induced hypergastrinemia.

In man nizatidine is absorbed rapidly, peak plasma concentrations occur from 0.5 to 3 hours after an oral dose. Approximately 90% of an oral dose of nizatidine is excreted in the urine within 12 hours, with about 60% as unchanged drug. The elimination half-life is one to two hours and the systemic plasma clearance is about 50 L/hour. Antacids consisting of aluminum and magnesium hydroxides with simethicone decrease absorption of nizatidine by about 10%. With food the AUC and Cmax increase by approximately 10%. Renal impairment significantly prolongs the half-life and decreases the clearance of nizatidine.

INDICATIONS AND USAGE

phl-NIZATIDINE (nizatidine) is indicated in the treatment of conditions where a controlled reduction of gastric acid secretion is required such as, for ulcer healing and/or pain relief: acute duodenal ulcer, acute benign gastric ulcer, gastroesophageal reflux disease, and prophylactic use in duodenal ulcer.

CONTRAINDICATIONS

phl-NIZATIDINE (nizatidine) is contraindicated for patients with known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including phl-NIZATIDINE, should not be administered to individuals with a history of previous hypersensitivity to other agents.

PRECAUTIONS

Use in Gastric Ulcer:

Where gastric ulcer is suspected the possibility of malignancy should be excluded before therapy with phl-NIZATIDINE (nizatidine) is instituted.

Use in Pregnancy and Lactation:

The safety of phl-NIZATIDINE during pregnancy has not been established. Reproduction studies performed in rats and rabbits at doses up to 300 times the human dose have revealed no evidence of impaired fertility or teratogenicity. If the administration of phl-NIZATIDINE is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the fetus. Nizatidine is secreted in human breast milk in proportion to maternal plasma concentrations (<0.1%), and caution should be exercised when phl-NIZATIDINE is administered to nursing mothers.

Use in Impaired Renal Function:

As nizatidine is excreted via the kidney, dosage should be adjusted in patients with moderately or severely impaired renal function (See Dosage and Administration).

Use in Hepatic Dysfunction:

Nizatidine is partially metabolized in the liver; however, in patients with mild to moderate hepatic dysfunction, disposition of nizatidine is similar to that of normal subjects.

Use in Elderly Patients:

Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone is not an important factor in determining the disposition of nizatidine. However elderly patients may have reduced renal function (see Dosage and Administration).

Pediatric Use:

The safety and effectiveness of nizatidine in children has not been established.

Laboratory Tests:

False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions:

No interactions have been observed between phl-NIZATIDINE and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, warfarin, aminophylline, diazepam, and metoprolol. phl-NIZATIDINE does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of ASA daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

ADVERSE REACTIONS

Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. North American placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among the more common adverse events in these placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs less than 0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A

variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic:

Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine. In some cases there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and in a single instance SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to 3 times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo treated patients. Hepatitis and jaundice have been reported. All abnormalities were reversible after discontinuation of phl-NIZATIDINE (nizatidine).

Cardiovascular:

In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered nizatidine and in 3 untreated subjects.

Central Nervous System:

Rare cases of reversible mental confusion have been reported.

Endocrine:

Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to phl-NIZATIDINE. Impotence and decreased libido were reported with equal frequency by patients who received phl-NIZATIDINE and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic:

Fatal thrombocytopenia was reported in a patient who was treated with

phl-NIZATIDINE and another H_2 receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental:

Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity:

As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonist should not be administered to individuals with a history of previous hypersensitivity to these agents Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other:

Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever and nausea related to nizatidine administration have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is little clinical experience with deliberate overdosage of phl-NIZATIDINE (nizatidine) in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Should overdosage occur, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

DOSAGE AND ADMINISTRATION

Duodenal or Gastric Ulcer:

One 300 mg capsule or two 150 mg capsules once daily at bedtime. Alternatively 150 mg twice daily may be used.

Healing occurs within 4 weeks in most cases of duodenal ulcer; but if healing is not documented or has not occurred, therapy should be given for 8 weeks.

Maintenance Therapy in Duodenal Ulcer:

One 150 mg capsule once daily at bedtime for 6 - 12 months depending on the severity of the condition.

Gastroesophageal Reflux Disease:

One 150 mg capsule twice daily for the treatment of erosions, ulcerations, and associated heartburn.

Antacids may be given concomitantly if needed.

Dosage Adjustment in Renal Impairment:

Renal Function	Creatinine Clearance (mL/min.)	Dosage	
		Acute	Maintenance
Normal	> 50	300 mg/day	150 mg/day
Moderate Impairment	20-50	150 mg/day	150 mg/2nd day
Severe Impairment	< 20	150 mg/2nd day	150 mg/3rd day

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

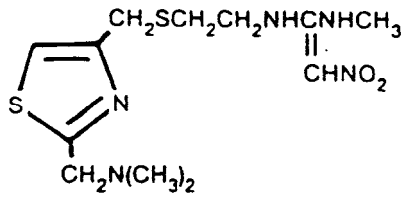
Brand Name: phl-NIZATIDINE

Proper Name: Nizatidine

Chemical Name: N-[2-[[[2-[(Dimethylamino) methyl]-4-thiazolyl]-methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine.

1,1-Ethenediamine, N-[2-[[[2-[(dimethylamino) methyl]-4-thiazolyl]methyl]thio]ethyl]-N'-methyl-2-nitro-

Structural Formula:



Molecular Formula: $C_{12}H_{21}N_5O_2S_2$

Molecular Weight: 331.46

Description: Nizatidine is a lipophobic, off-white to buff crystalline solid.

Melting Point: 130-131.5°C

pKa: Dimethylformamide 66%: 6.25, 8.4 ; Water: 2.1, 6.8

pH: Aqueous 1% Solution: 9.0

COMPOSITION:

phl-NIZATIDINE (nizatidine) 150 mg capsules also contain corn starch, magnesium stearate and silicone. The capsule shells contain Benzyl Alcohol, Carboxymethylcellulose Sodium, Edetate Calcium Disodium, Gelatin, Iron Oxide Yellow, Parabens (Benzyl, Propyl and Methyl), Sodium Lauryl Sulfate, Sodium Propionate and Titanium Dioxide.

phl-NIZATIDINE (nizatidine) 300 mg capsules also contain corn starch, povidone, carboxymethyl cellulose sodium, silicone and talc. The capsule shells contain Benzyl Alcohol, Carboxymethylcellulose Sodium, Edetate Calcium Disodium, Gelatin, Iron Oxide Yellow, Parabens (Benzyl, Propyl and Methyl), Sodium Lauryl Sulfate, Sodium Propionate and Titanium Dioxide.

STABILITY AND STORAGE RECOMMENDATIONS:
Store at 15° - 30°C.

AVAILABILITY OF DOSAGE FORMS

phl-NIZATIDINE (nizatidine) 150 mg: Each capsule is made of an opaque yellow cap and a lighter yellow opaque body. The cap is printed in black ink with "*ab*", and the body is printed in black ink with "N 150". Each capsule contains 150 mg of nizatidine and is available in HDPE bottles of 100.

phl-NIZATIDINE (nizatidine) 300 mg: Each capsule is made of an opaque yellow cap and a lighter yellow opaque body. The cap is printed in black ink with "*ab*", and the body is printed in black ink with "N 300". Each capsule contains 300 mg of nizatidine and is available in HDPE bottles of 100.

phl-NIZATIDINE is a Schedule F drug and cannot be obtained without a written order from a licenced practitioner.

PHARMACOLOGY

ANIMAL:

Nizatidine is a competitive, reversible, selective antagonist of the histamine H_2 receptors of the rat uterus and the oxyntic cells of the dog stomach.

In the conscious dog with a Heidenhain pouch, nizatidine given orally or intravenously antagonized gastric acid secretion induced by histamine, gastrin and methacholine. It was 5 to 10 times more active than cimetidine in this respect.

Nizatidine was well absorbed from all segments of the dog's small intestine; the ratio of ED_{50} P.O. to ED_{50} I.V. for inhibition of maximal response to histamine was 2.2. Identical molar doses of nizatidine given I.V., I.M., or S.C. were equal in peak effect against histamine-induced gastric acid secretion. Nizatidine was more active and exhibited a longer duration of action than cimetidine on food-induced gastric secretion in the dog.

At equi-potent doses of cimetidine and nizatidine, both the binding affinity of nizatidine for the histamine H_2 receptors of the gastric mucosa of the bullfrog and the duration of inhibition of histamine-stimulated acid secretion were significantly greater than those of cimetidine.

The correlations between peak inhibition of histamine-induced acid secretion and log-dose of nizatidine ($R = 0.93$), and peak plasma concentration and log-dose of nizatidine ($R = 0.88$) were highly significant.

Dogs receiving nizatidine at oral doses of 5 μmol/kg twice daily did not develop tolerance to the antisecretory effects in a 15-day study.

The N-desmethylated metabolite of nizatidine had 61% of the activity of nizatidine on maximal gastric response to histamine. The sulfoxide derivative of nizatidine was inactive.

On a molar basis, the cytoprotective effect of nizatidine on gastric lesions induced by pyloric ligation and aminoguanidine, or HCl and ASA was at least 5 times greater than cimetidine.

Nizatidine does not stimulate receptors in isolated smooth and cardiac muscle preparations of the guinea pig and rat. In anesthetized dogs given I.V. nizatidine, heart rate and cardiac output were slightly decreased, while stroke volume was slightly increased. Other cardiovascular and respiratory parameters were not altered. Nizatidine given orally to rats is devoid of effects on renal function as estimated by changes in the excretion of urine, electrolytes, and creatinine. Nizatidine given orally or I.P. had no effect on extensor convulsions induced by pentylenetetrazole or electric shock, acetic acid-induced writhing, or hexobarbital sleeping time in mice.

Nizatidine has no competitive binding to high affinity, low capacity androgen receptor sites. Nizatidine as tested in rats does not have anti-androgen activity, nor an effect on plasma concentrations of androgen, nor any significant effect on prolactin release.

Nizatidine has no significant effect on the liver weight or cytochrome P-450 content in rats. Nizatidine weakly inhibits N-demethylation of ethylmorphine by hepatic microsomes by means of non-competitive inhibition kinetics. Cimetidine is a potent inhibitor characterized by mixed inhibition kinetics.

Absorption, Distribution, Metabolism and Elimination:

Pharmacokinetic studies using radiocarbon-labelled drug have shown nizatidine to be rapidly absorbed from the gastrointestinal tracts of fasted rats and dogs. Maximum plasma concentrations of nizatidine were achieved within 30 minutes of oral administration of 10 mg/kg to rats and 5 mg/kg to dogs. The apparent plasma half-life of nizatidine in these

species was 1.1 and 1.5 hours, respectively, while the half-life of total radiocarbon, representing unaltered nizatidine and metabolites was 3.4 and 2.8 hours, respectively. Food hindered nizatidine absorption in the rat. The half-life of nizatidine in the fed animal was 2.6 hours. The absolute bioavailability of nizatidine in the dog for a 5 mg/kg dose was 82%.

Nizatidine was excreted by both renal and biliary routes, the former being the major route in the rat and dog. Unaltered nizatidine was the major component in the urine and bile of rats and in the urine of dogs. Minor metabolites eliminated by the rat included N-desmethyl nizatidine, nizatidine sulfoxide, and nizatidine N-oxide. The minor metabolites in dog urine were nizatidine N-oxide, nizatidine N-desmethyl, and nizatidine sulfoxide.

Radiocarbon levels in male rats after oral administration of a single dose of 10 mg/kg of ^{14}C-nizatidine, in all tissues with the exception of liver and kidney (organs involved directly in metabolism and elimination) were comparable to levels found in the plasma. The half-life of radiocarbon in most tissues was not significantly different than that achieved in the plasma.

HUMAN:

Nizatidine is absorbed rapidly after oral administration. Peak plasma concentrations occur from 0.5 to 3 hours after the dose. Absorption is unaffected by food or propantheline. However, antacids decrease the absorption of nizatidine by about 10%. The absolute oral bioavailability of nizatidine is 70.9% $\pm$ 6.4. Approximately 35% of nizatidine is bound to plasma protein, primarily 1-glyco-protein. This binding is not influenced by other drugs such as warfarin, diazepam, acetaminophen, propranolol, or phenobarbital. Approximately 90% of an oral dose of nizatidine is excreted in the urine within 12 hours. About 60% of an oral dose and about 77% of an I.V. dose of nizatidine is excreted as unchanged drug.

The elimination half-life is one to two hours and the systemic plasma clearance is about 50 L/hour. The volume of distribution is 0.8 to 1.5ÊL/kg. Since nizatidine is primarily excreted

in the urine, renal impairment significantly prolongs the half-life and decreases the clearance of nizatidine. In anephric individuals with creatinine clearance less than 10 mL/min., the half-life is 3.5 to 11 hours, and the plasma clearance is 7 to 14 L/hour. The pharmacokinetic profile for nizatidine in the elderly was not significantly different from the profile in younger normal subjects.

Gastric acid suppression correlates directly with nizatidine doses from 75 to 350 mg. Oral doses of 100 mg or 1.3 mg/kg suppressed gastric acid secretion in sham fed volunteers for 3 hours after the dose. The duration of acid suppression directly correlates with the nizatidine dose. 300 mg nizatidine suppressed acid secretion almost entirely early in the day, and the suppression persisted about 10 hours. Nocturnal acid was suppressed for 10 to 12 hours after 300 mg nizatidine.

Treatment for up to 2 weeks with nizatidine 600 mg daily did not influence the serum concentrations of gonadotropins, prolactin, growth hormone, antidiuretic hormone, cortisol, triiodothyronine, thyroxin, testosterone, 5 - α dihydro- testosterone, androstenedione or estradiol.

TOXICOLOGY

Acute Toxicity:

Species	Route	Sex	No. of Animals	Nizatidine LD_{50} (mg/kg)
Mouse	Oral	M	50	1689
		F	50	1630
	I.V.	M	60	236
		F	50	232
	S.C.	M	50	1174
		F	50	1082
Rat	Oral	M	60	2240
		F	50	1653
	I.V.	M	40	301
		F	50	301
	S.C.	M	20	>2000(LD_0)
		F	20	
Dog	Oral	M	4	>800(LD_0)
		F	4	
	I.V.	M	2	>75(LD_0)
		F	2	
	I.M.	M	2	>225(LD_0)
		F	2	
Monkey	Naso-gastric	M	2	>1200(LD_0)
		F	2	
	I.V.	M	2	>200(LD_0)
		F	2	

Signs of toxicity included: vomiting, salivation, vasodilation, ptosis, tremors, hypoactivity, diarrhea, ataxia and lacrimation.

The recommended human dose is $\leq$ 5 mg/kg/day.

Subacute Toxicity:

Mice (5/sex/dose) were maintained on diets containing 0, 0.225, 0.45, 0.9, or 1.8% nizatidine for 14 days. All animals survived. There were no physical signs of toxicity, or toxicologically

significant changes in hematologic or serum chemistry parameters. There was a slight increase in liver weight at the 1.8% treatment level.

Mice were maintained for 3 months on diets containing 0, 0.05, 0.3 or 1.5% nizatidine. All mice receiving nizatidine survived. Female mice had slight dose-related decreases in mean body weight gains. An increase in liver weight at the 1.5% treatment level was seen.

Rats fed nizatidine at doses of 0.225% or 1.0% (ca. 169, or 773 mg/kg/day) for three months had minor toxicological changes including decreased body weight gain, food consumption, and efficiency of food utilization. There was no evidence of adverse effects in rats receiving 0.05% (ca. 38 mg/kg/day) for three months.

Dogs given up to 800 mg/kg/day orally for two weeks experienced vasodilatation, lacrimation, and vomition. One dog receiving 800 mg/kg/day had an elevated leukocyte count and an increased serum alanine transaminase activity.

Dogs survived oral doses up to 800 mg/kg/day of nizatidine for three months without significant impairment of tissue or organ systems. Treatment-related effects included slight decreases in hemoglobin and associated erythrocytic parameters, decreased hepatic p-nitroanisole O-demethylase activity, and a significant reduction in body weight for one female at the 800 mg/kg/day nizatidine treatment level.

Chronic Toxicity:

Nizatidine was given daily to rats (20/sex/dose) for six months at dietary levels of 0, 0.05%, 0.225%, or 1.0% (ca. 0, 30, 136 and 617 mg/kg). Physical signs of toxicity were perineal soiling in females receiving 0.225% and 1.0%, and decreased mean body weight gains for females receiving 0.225% and both sexes receiving 1% nizatidine. Efficiency of food utilization was decreased for rats at the 1% treatment level. Increases occurred in the

weights of livers from males receiving 0.225% and in the livers and kidneys from males and females at the 1% nizatidine treatment level.

Rats were maintained for 1 year at dietary levels of 0, 0.05%, 0.225% and 1.0% nizatidine (ca. 0, 27, 121, and 544 mg/kg/day). The highest dose was approximately 110 times the recommended human dose. The minor toxicological changes that occurred were similar to the three and six-month studies.

Beagle dogs (4/sex/dose) received daily oral doses of 0, 50, 140 or 400Êmg/kg/day for one year. The highest dose was 80 times the recommended human dose. Physical signs of toxicity were similar to those seen in previous subchronic studies. Additional signs of toxicity were diarrhea, blood in feces, miosis with or without increased pupillary light reflex, decreased thrombocyte counts, and decreased hepatic microsomal enzyme activity and cytochrome P-450 content.

Reproductive Studies:

Adult female Fischer 344 rats (10/dose) received daily dietary doses of 0, 0.05, 0.225, or 1.0% nizatidine (ca. 0, 27, 119, or 506 mg/kg) for a two-week premating period and throughout breeding and gestation. Approximately double these dietary doses were provided during lactation. The females were mated with males from corresponding treatment groups that were assigned to the three-month subacute study. Food consumption and body weights decreased, as did progeny body weights. Coolness, dehydration and stickiness were observed in the progeny of treated dams. Due to the small sample sizes, lack of a dose-responsive relationship and high interlitter variability, meaningful evaluation of progeny survival data was not possible.

Adult female Wistar rats (10/dose) received daily dietary doses of 0, 0.01, 0.05, 0.225, and 1.0% (ca. 0, 7, 35, 155 and 680 mg/kg) for a two-week premating period. During gestation,

approximately 1.3-2 times those doses were administered during lactation. The females were mated with previously untreated males that received treated diets only during the mating period. Parental toxicity was expressed at the 1% treatment level as decreased food consumption and body weights. Progeny body weights were decreased only at the 1% treatment level. Progeny survival was not affected.

A two-generation fertility, perinatal, and postnatal study was conducted with 80 male and 160 female Wistar rats. The dose levels were 0, 0.05, 0.225 and 1.0% (ca. 0, 33, 143 and 648 mg/kg/day). Females of the F_0 generation showed decreased food consumption, body weight, and/or body weight gain. F_1 animals had slightly decreased body weights and food consumption.

Teratology:

Nizatidine was administered by oral gavage to 25 mated Wistar rats per dose level at doses of 0, 50, 275, and 1500 mg/kg/day on gestation days 6-15. Maternal effects were reduced food consumption and net body weight gain. There were no reproductive or fetal effects.

Groups of 20 pregnant Dutch Belted rabbits were given daily oral doses of 0, 50, 275, or 1500 mg/kg on gestation days 6-18. Two females from the 1500 mg/kg/day group died during the study. Loose stools, and/or bloody discharges, decreased body weight gain and decreased food consumption occurred at the 1500 mg/kg/day treatment level. Six animals from the 1500 mg/kg group aborted between gestation days 18 and 26 following anorexia and loss of body weight. The mean percent of live fetuses was decreased at the 1500 mg/kg dose level. Decreased fetal body weights and increased percent of abnormal fetuses attributed to runting were also noted, this indicated fetal growth retardation associated with severe maternal toxicity. There was no evidence of a teratogenic effect as defined as an increase in the incidence of frank structural malformations.

Nizatidine was administered by gavage to mated female New Zealand White rabbits (20 animals/group) at dose levels of 0, 50, 275, and 1000 mg/kg/day on gestation days 6 through 18. Maternal toxicity was indicated by decreased body weight and food consumption and an increased incidence of transient diarrhea or soft stool in the high-dose group. The no-effect level for maternal toxicity was 275 mg/kg/day. Fetal toxicity was indicated by decreased fetal weights, an increased incidence of fetal runts, and a trend toward increased fetal resportions in the high dose group. The no effect level for developmental toxicity was 275 mg/kg/day. There was no indication of nizatidine-induced teratogenicity.

Carcinogenicity:

Two year oral carcinogenicity studies with nizatidine in rats and mice revealed no carcinogenic response at doses up to 2175 mg/kg. These dose levels are equivalent to approximately 800 times the maintenance dose in man.

Mutagenicity:

The mutagenicity of nizatidine was evaluated in a battery of inÊvitro and inÊvivo tests utilizing bacterial mutation (Ames and Modified Ames tests), unscheduled DNA synthesis, sister chromatid exchange (I.P. and P.O. administration), and the mouse lymphoma assay. Nizatidine was found to have no mutagenic effect in each study.

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